ClinicalEvidence

Bacterial vaginosis

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ABSTRACT

INTRODUCTION: Bacterial vaginosis is characterised by large numbers of anaerobic bacteria in the vagina. However, the specific causative agents are unknown, and it may resolve spontaneously. The condition is asymptomatic in 50% of infected women. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of: different antibacterial regimens in non-pregnant women with symptomatic bacterial vaginosis on cure rates and symptom relief; antibacterial treatments in pregnant women to reduce adverse outcomes of pregnancy and prevent neonatal complications; treatments before gynaecological procedures? Does treating male partners prevent recurrence? We searched: Medline, Embase, The Cochrane Library and other important databases up to June 2006 (BMJ Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 27 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: clindamycin, metronidazole, and oral or intravaginal antibacterial treatment.

QUESTIONS

INTERVENTIONS

Key points

- Bacterial vaginosis is characterised by large numbers of anaerobic bacteria in the vagina, causing a grey, fishy smelling discharge in half of affected women. However, the specific causative agents are unknown and it may resolve spontaneously.

  Bacterial vaginosis is very common, especially in women using intrauterine contraceptive devices, with new or multiple partners and in lesbians.

  Bacterial vaginosis is associated with increased complications in pregnancy, endometritis, and increased risks of HIV infection.

- Antibiotic treatment with metronidazole and clindamycin increases cure rates compared with placebo in non-pregnant women.

Intravaginal clindamycin may reduce systemic adverse effects, but has been associated with mild to severe colitis and vaginal candidiasis.

We don't know which is the most effective antibiotic regimen, or what the long term effects of treatment might be.

More than 50% of women may have recurrence within 2 months of antibiotic treatment.

- In pregnant women with bacterial vaginosis, oral or vaginal antibiotics have not been shown overall to reduce complications of pregnancy, although studies have given conflicting results.

  Studies using higher doses of antibiotics, and where courses started earlier in pregnancy, are most likely to show a benefit.

  Treatment of women with clinically equivocal bacterial vaginosis may increase the risks of preterm birth and low birth weight.

- Treating the woman's male sexual partner with metronidazole or clindamycin does not reduce the risk of recurrence in the woman.

- In women with bacterial vaginosis who are about to undergo surgical abortion, antibiotics may reduce the risk of subsequent pelvic inflammatory disease, but we don't know if they are beneficial before other procedures.

DEFINITION

Bacterial vaginosis is a microbial disease characterised by a change in the bacterial flora of the vagina from mainly *Lactobacillus* species to high concentrations of anaerobic bacteria. The condition is asymptomatic in 50% of infected women. Women with symptoms have an excessive white to grey, or malodorous vaginal discharge, or both; the odour may be particularly noticeable during sexual intercourse. Commonly practised clinical diagnosis requires three out of four features: the presence of clue cells on microscopy; a homogenous discharge adherent to the vaginal walls; pH of vaginal fluid greater than 4.5; and a “fishy” amine odour of the vaginal discharge before or after addition of 10% potassium hydroxide. Some experts prefer other methods of diagnosis, (e.g. Gram stain of vaginal secretions), particularly in a research setting. Gram stain using Nugent's criteria [1] categorise the flora of vagina into three categories — normal, intermediate, and flora consistent with bacterial vaginosis. Abnormal vaginal flora includes intermediate flora and bacterial vaginosis.

INCIDENCE/ PREVALENCE

Bacterial vaginosis is the most common infectious cause of vaginitis, being about twice as common as candidiasis. [2] Prevalences of 10–61% have been reported among unselected women from a range of settings. [3] Data on incidence are limited but one study found that, over a 2 year period, 50% of women using an intrauterine contraceptive device had at least one episode, as did 20% of women using oral contraceptives. [4] Bacterial vaginosis is particularly prevalent among lesbians. [5]

AETIOLOGY/ RISK FACTORS

The cause of bacterial vaginosis is not fully understood. Risk factors include new or multiple sexual partners [2] [4] [6] and early age of sexual intercourse, [7] but no causative microorganism has been shown to be transmitted between partners. Use of an intrauterine contraceptive device [4] and douching [6] have also been reported as risk factors. Infection seems to be most common around the time of menstruation. [8]

PROGNOSIS

The course of bacterial vaginosis varies and is poorly understood. Without treatment, symptoms may persist or resolve in both pregnant and non-pregnant women. Recurrence after treatment occurs in about a third of women. A history of bacterial vaginosis is associated with increased rates of complications in pregnancy: low birth weight; [7] preterm birth (pooled OR from 10 cohort studies: 1.8, 95% CI 1.5 to 2.6); [9] preterm labour; premature rupture of membranes; [7] late miscarriage; chorioamnionitis; [10] endometritis after normal delivery (8.2% *v* 1.5%; OR 5.6, 95% CI 1.8 to 17.2); [11] endometritis after caesarean section (55% *v* 17%; OR 5.8, 95% CI 3.0 to 10.9); [12] and surgery to the genital tract. [13] [14] Women who have had a previous preterm delivery are especially at risk of complications in pregnancy, with a sevenfold increased risk of preterm birth (24/428 [5.6%] in all women *v* 10/24 [41.7%] in women with a previous preterm birth). [15] Bacterial vaginosis can also increase the risk of HIV acquisition and transmission. [16]

AIMS OF INTERVENTION

To alleviate symptoms and to prevent complications relating to childbirth, termination of pregnancy, and gynaecological surgery, with minimal adverse effects; to reduce adverse neonatal outcomes.

OUTCOMES

Preterm delivery; other complications in pregnancy; puerperal and neonatal morbidity and mortality; clinical or microbiological cure rates, usually at 1–2 weeks or 4 weeks after completing treatment; recurrence rates.

METHODS

Clinical Evidence search and appraisal March 2004. In addition, the authors used information obtained from drug manufacturers. The following databases were used to identify studies for this

chapter - Medline 1966 to June 2006, Embase 1980 to June 2006 and The Cochrane Library 2006 Issue two. Additional searches were carried out using the websites - NHS Centre for Reviews and Dissemination (CRD), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA), Turning Research into Practice (TRIP) and National Institute of Health and Clinical Excellence guidance (NICE). Abstracts of the studies retrieved were assessed independently by two information specialists using pre-determined criteria to identify relevant studies. Design criteria included: systematic reviews and RCTs in any language that were at least single blind, containing more than 20 individuals and with a follow up of more than 80%. There was no minimum length of follow up. We excluded all studies described as 'open', 'open label' or non-blinded.We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

QUESTION **What are the effects of different antibacterial regimens in non-pregnant women with symptomatic bacterial vaginosis on cure rates and symptom relief?**

OPTION ANTIBACTERIAL TREATMENT

Cure rates

Compared with placebo Intravaginal antibacterial treatment with clindamycin cream or metronidazole gel is more effective at increasing cure rates at 25–39 days compared with placebo (moderate-quality evidence).

Intravaginal antibacterials compared with oral antibacterials Intravaginal antibacterials (clindamycin cream, metronidazole gel) may be no more effective at increasing cure rates at 5–10 days or at 4 weeks compared with the oral antibacterial metronidazole (very low-quality evidence).

Twice-daily oral metronidazole regimen compared with single dose A twice-daily regimen of the oral antibacterial metronidazole is more effective at increasing cure rates at 7 days compared with a single dose (high-quality evidence).

Oral clindamycin compared with metronidazole Clindamycin may be no more effective at increasing cure rates at 7–10 days compared with metronidazole (low-quality evidence).

Once-daily intravaginal metronidazole gel compared with twice-daily dosing Once-daily dosing of intravaginal metronidazole has a similar cure rate to twice-daily dosing in women with antibacterial vaginosis (high-quality evidence).

Three days' treatment with intravaginal clindamycin ovules compared with 7 days' treatment with intravaginal clindamycin cream A 3-day course of intravaginal clindamycin ovules has a similar cure rate at 35 days to a 7-day course with intravaginal clindamycin cream (high-quality evidence).

Adverse effects

Recurrence of antibacterial vaginosis is likely to occur after antibacterial treatment. Intravaginal clindamycin has been associated with mild to severe colitis, and with vaginal candidiasis. Oral metronidazole has been associated with nausea and metallic taste.

For GRADE evaluation of interventions for bacterial vaginosis see table, p 13 .

Benefits:

Intravaginal antibacterial treatment versus placebo:

We found one systematic review (search date 1996, 4 RCTs, 406 women) comparing antibacterial treatment versus placebo. [17] It found that more women using intravaginal clindamycin cream and intravaginal metronidazole gel achieved cure than women using placebo (cumulative cure rates: 82% with intravaginal clindamycin cream *v* 35% with placebo at 25–39 days after completion of treatment; 2 RCTs, P value and CI not reported; 71% with intravaginal metronidazole gel *v* 50% with placebo at 28–32 days after completion of treatment; 2 RCTs, P value not reported). The relatively high cumulative cure rates with placebo treatment suggest that bacterial vaginosis often resolved spontaneously without treatment. [17]

Oral antibacterial treatment versus placebo:

We found no RCTs.

Intravaginal versus oral antibacterial treatment:

We found one systematic review (search date 1996, 5 RCTs, 741 women) [17] and one subsequent RCT [18] comparing intravaginal versus oral formulations of metronidazole and clindamycin. Three RCTs were conducted in symptomatic non-pregnant women and two were conducted in symptomatic and asymptomatic non-pregnant women. [17] The review found no significant difference in cumulative cure rates 5–10 days after completing treatment (85% with clindamycin vaginal cream 5 g at bedtime for 7 days *v* 81% with metronidazole vaginal gel 5 g twice daily for 5 days *v* 86% with oral metronidazole 500 mg twice daily for 7 days ; P values and CI not reported). Four weeks after completing

treatment, the cumulative cure rates were 82% for clindamycin vaginal cream, 71% for metronidazole vaginal gel, and 78% for oral metronidazole (P values not reported). The subsequent RCT (399 women) comparing intravaginal clindamycin cream versus oral metronidazole also found no significant difference in cure rates (68% with clindamycin cream *v* 67% with oral metronidazole; P = 0.81). [18] However, a large number of women (166/399 [42%]) were not included in the efficacy analysis making interpretation of the results difficult (results reported on 233 women, many exclusions for different reasons).

Different oral antibacterial regimens:
We found one systematic review (search date 1993 [19] updated in 1996 [17]), which identified four RCTs comparing oral metronidazole 500 mg twice daily for 7 days versus a single 2 g dose of metronidazole. [17] We also found two additional RCTs comparing metronidazole 500 mg twice daily for 7 days versus clindamycin 300 mg twice daily for 7 days. [20] [21] The systematic review found significantly higher cumulative cure rates with 7 day metronidazole than with single dose metronidazole at 3–4 weeks after completing treatment (82% with 7 days of metronidazole *v* 62% with single dose metronidazole; P < 0.05). [19] This conclusion remained the same when the review was updated. [17] The first additional RCT (143 symptomatic non-pregnant women) found no significant difference in cure rates within 7–10 days of starting treatment (women cured: 46/49 [94%] with clindamycin *v* 48/50 [96%] with metronidazole; RR 0.98, 95% CI 0.89 to 1.07). [20] A quarter of women were lost to follow up. The second RCT (96 non-pregnant women) found no significant difference in cure rates between clindamycin and metronidazole (39/41 [95%] with clindamycin *v* 41/44 [93%] with metronidazole; ARI 2%; RR 1.00, 95% CI 0.92 to 1.14). [21]

Different intravaginal antibacterial regimens:
We found no systematic review but found two RCTs. [22] [23] The first RCT (514 women) found no significant difference in cure rates between once daily and twice daily dosing of intravaginal metronidazole gel (118/207 [57%] with once daily gel *v* 129/209 [62%] with twice daily gel; RR 0.92, 95% CI 0.79 to 1.08). [22] The second RCT (662 women) compared 3 day treatment with intravaginal clindamycin ovules versus 7 day treatment with intravaginal clindamycin cream. [23] It found no significant difference in cure rates at 35 day assessment (134/238 [56%] with 3 day ovules *v* 113/224 [50%] with 7 day cream; ARI 6%; RR 1.10, 95% CI 0.94 to 1.30).

Harms:

Intravaginal antibacterial treatment versus placebo:
The review gave no information on adverse effects. [17]

Oral antibacterial treatment versus placebo:
We found no RCTs.

Intravaginal versus oral antibacterial treatment:
The RCT found no significant difference in the frequency of adverse effects between intravaginal clindamycin and oral metronidazole (10.3% with intravaginal clindamycin *v* 16.3% with oral metronidazole; P = 0.104). [18] Taste perversion (0% with intravaginal clindamycin *v* 3.1% with oral metronidazole; P value not reported) and nausea (1.0% with intravaginal clindamycin *v* 5.6% with oral metronidazole; P value not reported) accounted for most of the difference between the two treatment groups. Rates of vaginal candidiasis were similar between the two treatment groups (3.1% with oral metronidazole *v* 3.4% with intravaginal clindamycin; P value not reported). Comparison of results across RCTs found that yeast vulvovaginitis might be less common with intravaginal metronidazole than with oral metronidazole (4% for intravaginal [24] *v* 8–22% for oral [25]). Intravaginal clindamycin has been associated, rarely, with mild to severe colitis [26] and vaginal candidiasis [27] (vaginal candidiasis with 7 day treatment: 13.3% in pregnant women *v* 10.4% in non-pregnant women).

Different oral antibacterial regimens:
The review gave no information on adverse effects of 7 day or single dose oral metronidazole. [17]
The first RCT comparing oral clindamycin versus oral metronidazole reported nausea (7/49 [14%] with oral clindamycin *v* 10/50 [20%] with oral metronidazole; significance not reported) and metallic taste (0/49 [0%] with oral clindamycin *v* 3/50 [6%] with oral metronidazole; significance not reported). [20]

Different intravaginal antibacterial regimens:
The first RCT found no significant difference in the proportion of people who had adverse effects between once and twice daily intravaginal metronidazole gel (38% with once daily *v* 39% with twice daily; reported as non-significant, CI not reported). [22] Once or twice daily intravaginal metronidazole was associated with gastrointestinal symptoms in 7% of people in each group, vulvovaginal candidiasis in 7%, and symptoms of vaginal discharge in 11%. [22] The second RCT found that the proportion of people experiencing adverse effects was similar between 3 day clindamycin ovules and 7 day clindamycin cream, except for vaginal pain (3.4% with 3 day ovules *v* 0.9% with 7 day

cream; P value not reported), flu syndrome (0.9% with 3 day ovules *v* 2.7% with 7 day cream; P value not reported), and headache (6.4% with 3 day ovules *v* 3.6% with 7 day cream; P value not reported). [23] Most adverse effects were rated "mild to moderate" intensity (proportion of mild to moderate adverse effects: 177/186 [95%] with 3 day ovules *v* 149/171 [87%] with 7 day cream; proportion with severe adverse effects: 9/186 [5%] with 3 day ovules *v* 19/171 [11%] with 7 day cream; P value not reported).

Comment: Intravaginal administration reduces systemic absorption and systemic adverse effects. Some women may prefer oral medication because it is more convenient. Most of the RCTs followed women for a short period of time (about 4 weeks), therefore it is not possible to fully evaluate long term adverse effects and recurrence rates.

Recurrence:
We found one RCT (61 women, 19 withdrew) that followed up women who had been treated for bacterial vaginosis with either clindamycin vaginal cream or oral metronidazole. [28] It found that more than 50% of women in both groups had recurrent bacterial vaginosis 2 months after treatment (exact figures and statistical analysis not reported).

QUESTION What are the effects of antibacterial treatments in pregnant women to reduce adverse outcomes of pregnancy and prevent neonatal complications?

OPTION ANTIBACTERIAL TREATMENTS (EXCLUDING INTRAVAGINAL CLINDAMYCIN) IN PREGNANT WOMEN New

Complications
Compared with placebo Antibacterials may be no more effective at reducing the risk of preterm delivery, low birth weight, perinatal death, or neonatal sepsis in pregnant women with bacterial vaginosis compared with placebo or no treatment (very low-quality evidence).

Note
Treatment of pregnant women who have equivocal bacterial vaginosis may increase the risk of preterm birth and of low birth weight.

For GRADE evaluation of interventions for bacterial vaginosis, see table, p 13 .

Benefits: We found one systematic review (search date 2002, 10 RCTs, 4249 women) comparing antibacterial treatment versus placebo, [29] and two subsequent RCTs. [30] [31]

In all pregnant women:
The review performed separate analyses of any antibiotic, oral antibiotics, or intravaginal antibiotics versus placebo or no treatment; none found a significant difference in outcomes between antibacterial treatment and placebo or no treatment. [29] Overall, the review found no significant difference between any antibiotic and placebo or no treatment in the risk of preterm delivery, low birth weight, perinatal death, or neonatal sepsis in the general population of pregnant women with bacterial vaginosis (preterm delivery < 37 weeks' gestation, 8 RCTs, 4062 women: OR 0.93, 95% CI 0.78 to 1.12; low birth weight, 4 RCTs, 3131 women: OR 0.97, 95% CI 0.76 to 1.23; perinatal death, 2 RCTs, 749 women: OR 2.26, 95% CI 0.68 to 7.46; neonatal sepsis, 2 RCTs, 428 women: 0.95, 95% CI 0.06 to 15.32). [29] Similarly, it found no significant difference in these outcomes between oral antibiotics and placebo or no treatment (preterm delivery < 37 weeks' gestation, 5 RCTs, 2996 women: OR 0.88, 95% CI 0.72 to 1.09; low birth weight, 3 RCTs, 2459 women: OR 0.90, 95% CI 0.69 to 1.17; perinatal death, 2 RCTs, 739 women: OR 2.03, 95% CI 0.67 to 6.13; neonatal sepsis, 1 RCT, 406 women: OR 0.95, 95% CI 0.06 to 15.28). It also found no significant difference in these outcomes between intravaginal antibiotics and placebo or no treatment (preterm delivery < 37 weeks' gestation, 2 RCTs, 1056 women: OR 1.16, 95% CI 0.78 to 1.72; low birth weight, 1 RCT, 672 women: OR 1.35, 95% CI 0.77 to 2.36; perinatal death, no RCTs: OR and CI not estimable; neonatal sepsis, 1 RCT, 22 women: OR 1.01, 95% CI 0.33 to 3.06). [28] The first subsequent RCT (485 asymptomatic women with bacterial vaginosis) found that oral clindamycin given early in the second trimester significantly reduced the rate of miscarriage or preterm delivery compared with placebo (13/244 [5.3%] with clindamycin *v* 38/241 [15.8%] with placebo; ARR 10.4%, 95% CI 5.0% to 15.8%). [30] The second subsequent RCT (409 asymptomatic women with abnormal vaginal flora) found that 3 day treatment with intravaginal clindamycin cream at or before 20 weeks of gestation significantly decreased the rate of preterm birth compared with placebo (8/208 [4%] with intravaginal clindamycin *v* 19/201 [10%] with placebo; OR 0.38, 95% CI 0.16 to 0.90). [31] The second RCT did not analyze the results according to whether the women were at high risk (previous preterm birth). [31]

Harms:

General adverse effects:
Overall, the systematic review found that adverse effects of antibiotics were uncommon (although not all of the included RCTs gave information on adverse effects). [29] It found no significant difference between any antibiotic and placebo or no treatment in the risk of adverse effects (adverse effects sufficient to stop treatment, 2 RCTs, 965 women: OR 1.31, 95% CI 0.68 to 2.49; adverse effects not sufficient to stop treatment, 3 RCTs, 1340 women: OR 1.33, 95% CI 0.73 to 2.45). However, one large RCT (1953 women) included in the review found significantly more adverse effects with oral metronidazole compared with placebo, particularly gastrointestinal symptoms (20.0% with metronidazole *v* 7.5% with placebo; CI not reported). [32]

Comment:

The average quality of the RCTs in the systematic review was good. [29] All trials reported loss to follow up between 1–17% for the various treatment groups. The review found two different clusters of results for oral treatment of bacterial vaginosis among high risk women. Different effects may be because of differences in dose and type of treatment regimen or in the timing of treatment. [29]

Differences in oral treatment regimens:
Three RCTs included in the review [29] found that antibiotics reduced preterm birth, of which two [33] [34] used the US Centers for Disease Control and Prevention recommended treatment of bacterial vaginosis in pregnancy (oral metronidazole 250 mg 3 times daily for 7 days). The other [15] used a lower dose of oral metronidazole (400 mg twice daily for 2 days), but found a reduction in preterm birth in a small subgroup analysis (17 women in each group). One included RCT, which found no reduction in preterm birth, also used a lower dose of oral metronidazole (2 g single dose, repeated 48 hours later). [32] The subsequent RCT, which also found a benefit from treatment, used oral clindamycin, which has broader activity compared with metronidazole against bacterial vaginosis organisms (especially *Mobiluncus* species).

Differences in timing of treatment:
Differences in timing of treatment (early *v* late gestational age) may also have contributed to different results among RCTs. The two included RCTs [32] [35] that found no reduction in preterm birth initiated antibiotic treatment at about 24 weeks of gestation, but the subsequent RCT, which found a reduction in preterm birth, initiated antibiotic treatment earlier in the pregnancy (at about 16 weeks). [30] Unlike severely disturbed flora, intermediate flora is not considered altered sufficiently enough to be a microbiological diagnosis for bacterial vaginosis. [1] To a lesser degree, differences in study population (symptomatic *v* asymptomatic) and diagnosis of bacterial vaginosis (clinical *v* Gram stain diagnosis) may also have contributed to the differing results.

Diagnostic criteria and screening:
Bacterial vaginosis is a condition of altered vaginal flora. There is a continuum of degrees of alteration of vaginal flora that women may have, and bacterial vaginosis may be defined differently according to the diagnostic criteria being used. Given this uncertainty, screening for bacterial vaginosis may result in the treatment of some women who do not have bacterial vaginosis. Thus, it is important to evaluate the harms of treatment among women who have equivocal bacterial vaginosis. Subgroup analyses of RCTs suggest that likely harms of antibiotics in this group include an increase in preterm birth and low birth weight. [33] [36]

OPTION ANTIBACTERIAL TREATMENTS (EXCLUDING INTRAVAGINAL CLINDAMYCIN) IN PREGNANT WOMEN WHO HAVE HAD A PREVIOUS PRETERM BIRTH

Complications
Compared with placebo Antibacterials may reduce the risk of low birth weight in pregnant women who have had a previous preterm birth, but we don't know if they are more effective at reducing the risk of preterm delivery (very low-quality evidence).

Note
Treatment of pregnant women who have equivocal bacterial vaginosis may increase the risk of preterm birth, and of low birth weight.

For GRADE evaluation of interventions for bacterial vaginosis, see table, p 13 .

Benefits:

We found one systematic review (search date 2002, 10 RCTs, 4249 women) comparing antibacterial treatment versus placebo, [29] and one subsequent RCT. [30]

In women with previous preterm birth:
The review found that, in women who had a previous preterm birth, antibiotics significantly reduced the risk of low birth weight compared with placebo (2 RCTs of 114 women: OR 0.31, 95% CI 0.13 to 0.75). [29] However, antibiotics did not significantly reduce the risk of preterm delivery or perinatal death (preterm delivery < 37 weeks' gestation, 5 RCTs, 622 women: OR 0.83, 95% CI 0.59 to 1.17;

perinatal death, 2 RCTs, 155 women: OR 3.64, 95% CI 0.86 to 15.45), although results for preterm delivery varied widely among RCTs (see comment below). Subgroup analysis in the first subsequent RCT of women who had previous late miscarriage or preterm delivery found that fewer women taking oral clindamycin than placebo had late miscarriage and preterm delivery (miscarriage or preterm delivery: 7/36 [19%] with clindamycin *v* 16/38 [42%] with placebo; RR and CI not reported). [30]

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OPTION INTRAVAGINAL CLINDAMYCIN CREAM IN PREGNANT WOMEN New

Complications
Compared with placebo Intravaginal clindamycin may be no more effective than placebo at reducing the risks of preterm birth and low birth weight in women with bacterial vaginosis (very low-quality evidence).

Note
Treatment of pregnant women who have equivocal bacterial vaginosis may increase the risk of preterm birth, and of low birth weight.

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General adverse effects:
Overall, the systematic review found that adverse effects of antibiotics were uncommon (although not all of the included RCTs gave information on adverse effects). [29] It found no significant difference between any antibiotic and placebo or no treatment in the risk of adverse effects (adverse effects sufficient to stop treatment, 2 RCTs, 965 women: OR 1.31, 95% CI 0.68 to 2.49; adverse effects not sufficient to stop treatment, 3 RCTs, 1340 women: OR 1.33, 95% CI 0.73 to 2.45). However, one large RCT (1953 women) included in the review found significantly more adverse effects with oral metronidazole compared with placebo, particularly gastrointestinal symptoms (20.0% with metronidazole *v* 7.5% with placebo; CI not reported). [32] The first subsequent RCT found no significant difference in the proportion of women who had adverse effects, including gastrointestinal upset, nausea, vomiting, vulvovaginal candidiasis, and headache between intravaginal clindamycin and placebo (17/239 [7%] with intravaginal clindamycin *v* 8/239 [3%] with placebo; P = 0.10). [30] The second subsequent RCT gave no information on adverse effects.

Adverse outcomes of pregnancy and neonatal complications:
Three included RCTs found a non-significant increase in preterm birth in all risk women with bacterial vaginosis who used intravaginal clindamycin cream compared with placebo (first RCT, 271 women: 9/60 [15%] with clindamycin cream *v* 5/69 [7.2%] with placebo; reported as non-significant, RR and CI not reported; second RCT, 681 women: 51/340 [15.0%] with clindamycin cream *v* 46/341 [13.5%] with placebo; OR 1.1, 95% CI 0.7 to 1.7; third RCT, 375 women: 9/187 [5%] with clindamycin cream *v* 7/188 [4%] with placebo; OR 1.3, 95% CI 0.5 to 3.5). [37] [38] [39] Two included RCTs found that more women with bacterial vaginosis using intravaginal clindamycin had babies with low birth weight than women using placebo, although the difference was not significant (first RCT, 271 women: 8/59 [13.6%] with clindamycin cream *v* 3/69 [4.4%] with placebo; second RCT, 681 women: 30/334 [9.0%] with clindamycin cream *v* 23/338 [6.8%] with placebo; OR 1.3, 95% CI 0.8 to 2.4, reported as non-significant, RR not reported). [38]

Comment:

The average quality of the RCTs in the systematic review was good. [29] All trials reported loss to follow up between 1–17% for the various treatment groups. In addition to an increased risk of preterm birth and low birth weight with intravaginal clindamycin treatment, one included RCT found an alteration of normal vaginal flora to flora consistent with bacterial vaginosis among women at high risk of preterm birth who were treated with clindamycin cream. This alteration was reported as significant. [40]

Differences in timing of treatment:
Differences in timing of treatment (early *v* late gestational age) may also have contributed to different results among RCTs. The two included RCTs [32] [35] that found no reduction in preterm birth initiated antibiotic treatment at about 24 weeks of gestation, but the subsequent RCT, which found a reduction in preterm birth, initiated antibiotic treatment earlier in the pregnancy (at about 16 weeks).

[30] Another subsequent RCT found a reduction of preterm birth with intravaginal clindamycin treatment, initiated at or before 20 weeks of gestation. [31] However, the treatment was given for vaginal flora which included disturbances of intermediate abnormality as well as of severe abnormality. Unlike severely disturbed flora, intermediate flora is not considered altered sufficiently enough to be a microbiological diagnosis for bacterial vaginosis. [1] To a lesser degree, differences in study population (symptomatic *v* asymptomatic) and diagnosis of bacterial vaginosis (clinical *v* Gram stain diagnosis) may also have contributed to the differing results.

Diagnostic criteria and screening:
Bacterial vaginosis is a condition of altered vaginal flora. There is a continuum of degrees of alteration of vaginal flora that women may have, and bacterial vaginosis may be defined differently according to the diagnostic criteria being used. Given this uncertainty, screening for bacterial vaginosis may result in the treatment of some women who do not have bacterial vaginosis. Thus, it is important to evaluate the harms of treatment among women who have equivocal bacterial vaginosis. Subgroup analyses of RCTs suggest that likely harms of antibiotics in this group include an increase in preterm birth and low birth weight. [33] [36]

QUESTION Does treating male partners prevent recurrence?

OPTION TREATMENTS FOR PARTNERS TO PREVENT RECURRENCE

Recurrence rates
Treatment of male partner compared with no treatment Treating a steady male partner with oral antibacterials is no more effective at reducing the rate of recurring infections in women with bacterial vaginosis who are also receving antibacterial treatment than not treating the male partner (moderate-quality evidence).

For GRADE evaluation of interventions for bacterial vaginosis, see table, p 13 .

Benefits: We found one systematic review (search date not reported, 6 RCTs) evaluating the effect of treating male sexual partners of women with bacterial vaginosis on recurrence rates. [41] All RCTs identified by the review found that treating a sexual partner with metronidazole or clindamycin had no effect on recurrence rates in women with bacterial vaginosis receiving the same treatment (significance assessments not reported in the review). The RCTs identified by the review assessed a variety of treatment regimens and populations but excluded women who were pregnant or who had coexistent vaginal infections. The systematic review did not attempt to test for heterogeneity between RCTs or to pool the results.

Harms: The review found that treatment of male partners carries few physiological adverse effects. However, the authors suggested that emotional adverse effects may arise from implying that bacterial vaginosis is a sexually transmitted disease. [41] Adverse effects of metronidazole and clindamycin (oral or intravaginal) are reported elsewhere in this topic (see harms of antibacterial treatments, p 3).

Comment: The lack of evidence of effectiveness of both metronidazole and clindamycin suggests that anaerobes are unlikely to be the sole pathogenic agents linking bacterial vaginosis with sexual intercourse.

QUESTION What are the effects of treatment before gynaecological procedures?

OPTION ORAL OR INTRAVAGINAL ANTIBACTERIAL TREATMENT BEFORE SURGICAL ABORTION

Infection rates
Compared with placebo Treatment with antibacterials in women with bacterial vaginosis before surgical abortions is more effective than placebo at reducing the risk of acquiring infections (moderate-quality evidence).

Adverse effects
Intravaginal clindamycin has been associated with mild to severe colitis and vaginal candidiasis in non-pregnant women, and oral metronidazole has been associated with nausea and metallic taste.

For GRADE evaluation of bacterial vaginosis, see table, p 13 .

Benefits: We found no systematic review.

Before surgical abortion:
We found three RCTs. [13] [36] [41] The first RCT (174 women with bacterial vaginosis) compared oral metronidazole 500 mg 3 times daily for 10 days versus placebo in women about to have surgical abortion. [13] Fewer women taking oral metronidazole developed pelvic inflammatory disease

than those taking placebo, although the difference did not reach significance (3/84 [4%] with metronidazole *v* 11/90 [12%] with placebo; RR 0.29, 95% CI 0.08 to 1.01). The second RCT (1655 women) compared intravaginal clindamycin cream versus placebo in women about to have surgical abortion. [42] It found that significantly fewer women treated with intravaginal clindamycin had an infection after abortion (3/181 [1.7%] with clindamycin *v* 12/181 [6.6%] with placebo; RR: 0.24, 95% CI 0.07 to 0.86). The third RCT compared a single dose metronidazole suppository 2 mg versus placebo. [43] It found that fewer women using metronidazole suppository had postoperative upper genital tract infection, although the difference was not signficant (12/142 [8%] with metronidazole *v* 21/131 [16%] with placebo; RR 0.52, 95% CI 0.27 to 1.02). The broad confidence interval suggests that the RCT was underpowered to rule out clinically important differences.

Harms: The RCTs gave no information on adverse effects. [13] [42] [43] Adverse effects of metronidazole and clindamycin (oral or intravaginal) are reported elsewhere in this review. (see harms of antibacterial treatments in non-pregnant women, p 3).

Comment: Despite the non-significant findings of infections after abortion and operations, [13] [43] the trend in all trials was toward reduced infections among women receiving antibiotics. These trend need to be confirmed in trials with sufficient sample size to reach a conclusion.

OPTION ANTIBACTERIAL TREATMENT BEFORE GYNAECOLOGICAL PROCEDURES OTHER THAN ABORTION New

We found no direct information about the effects of antibacterial treatment in women with bacterial vaginosis about to have gynaecological procedures other than an abortion.

For GRADE evaluation of bacterial vaginosis, see table, p 13 .

Benefits: We found no systematic review.

Before gynaecological surgery:
Cohort studies suggest that bacterial vaginosis is associated with an increased risk of endometritis after caesarean section and vaginal cuff cellulitis after abdominal hysterectomy, [12] [14] but we found no RCTs of antibacterial treatment in women before such surgery.

Before insertion of an intrauterine contraceptive device:
Observational evidence suggests that bacterial vaginosis is associated with pelvic inflammatory disease (see pelvic inflammatory disease) in women using intrauterine contraceptive devices, [4] but we found no RCTs of antibacterial treatment in women with bacterial vaginosis before insertion of these devices.

Harms: The RCTs gave no information on adverse effects. [13] [42] [43] Adverse effects of metronidazole and clindamycin (oral or intravaginal) are reported elsewhere in this topic. (see harms of antibacterial treatments in non-pregnant women, p 3).

Comment: Despite the non-significant findings of infections after abortion and operations, [13] [43] the trend in all trials was toward reduced infections among women receiving antibiotics. These trend need to be confirmed in trials with sufficient sample size to reach a conclusion.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect
Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

New option added Antibacterial treatments (excluding intravaginal clindamycin) in pregnant women.
New option added Intravaginal clindamycin cream in pregnant women.
New option added Antibacterial treatment before gynaecological procedures other than abortion.

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TABLE **GRADE evaluation of interventions for bacterial vaginosis**

Important outcomes	Cure rates, symptom relief, recurrence, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of different antibacterial regimens in non-pregnant women with symptomatic bacterial vaginosis on cure rates and symptom relief?									
4 (406) [17]	Cure rates	Intravaginal antibacterial treatment *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
6 (974) [17] [18]	Cure rates	Intravaginal antibacterials *v* oral antibacterials	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for inclusion of different disease states and exclusion of participants in analysis
4 (?) [17] [19]	Cure rates	Oral metronidazole regimens *v* each other	4	0	0	0	0	High	
2 (184) [20] [21]	Cure rates	Oral clindamycin *v* metronidazole	4	–2	0	0	0	Low	Quality points deducted for poor follow-up and sparse data
1 (416) [22]	Cure rates	Once-daily *v* twice-daily dosing (metronidazole gel)	4	0	0	0	0	High	
1 (462) [28]	Cure rates	3 days' *v* 7 days' treatment (clindamycin)	4	0	0	0	0	High	
What are the effects of antibacterial treatments in pregnant women to reduce adverse outcomes of pregnancy, and prevent neonatal complications?									
27 (14,209) [28] [29] [30]	Complications	Antibacterials *v* placebo (all pregnant women)	4	–2	–1	–2	0	Very low	Quality points deducted for incomplete reporting of results and poor follow-up. Consistency point deducted for conflicting results. Directness points deducted for differences in disease states and diagnosis
10 (1265) [29] [30]	Complications	Antibacterials *v* placebo (pregnant women with previous preterm birth)	4	–2	–1	–2	0	Very low	Quality points deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for differences in disease states, antibiotics, and doses used between groups in comparison
7 (1594) [31] [37] [38] [39]	Complications	Intravaginal clindamycin *v* placebo	4	–1	–1	–1	0	Very low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results. Directness point deducted for uncertainty about diagnosis
Does treating male partners prevent recurrence?									
6 (?) [41]	Recurrence	Treatment of male partners *v* no treatment	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatment before gynaecological procedures?									
3 (809) [13] [42] [43]	Infection rates	Antibacterials *v* placebo	4	0	–1	0	0	Moderate	Quality point deducted for conflicting results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio